VoxelBox v5.0.5

1) Introduction and functions performed by VoxelBox

VoxelBox is a one-click Resting-State fMRI processing solution. VoxelBox integrates best-in-breed tools for each of the preprocessing tasks that its workflow covers. VoxelBox allows for full Automation of all the steps and enables a single-click pre-processing interface.

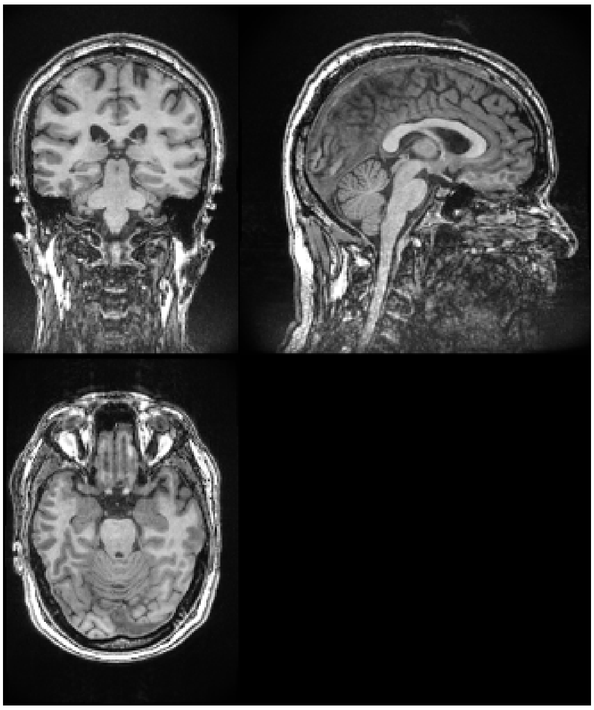
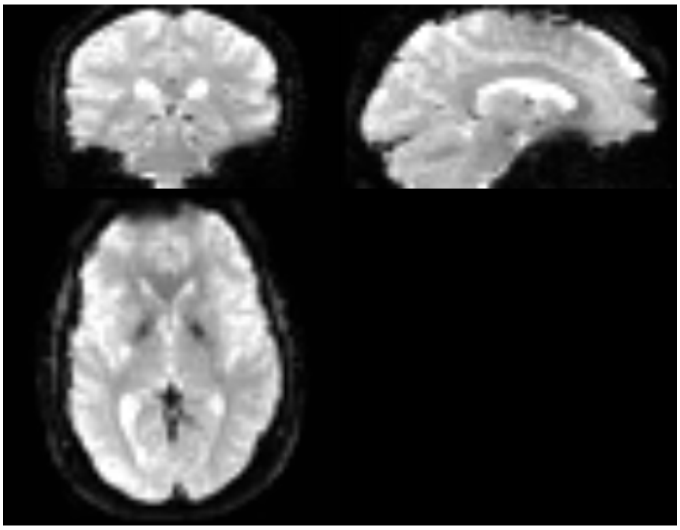
2) Details of preprocessing steps, libraries in use, and standards

Quality Assurance: Inspection of source images

- Individual slices in an fMRI acquisition commonly suffer from random variations in average signal intensity, noise spikes, ghosts, and data glitches. These may result from physiological sources (patient motion, respiration, cardiac pulsations, anxiety, drowsiness, drugs) or from the scanner itself (field inhomogeneities, eddy currents, gradient heating, electronics).

Unprocessed rs-fMRI and structural MRI scan

- Raw structural MRI and resting-state functional MRI scans.

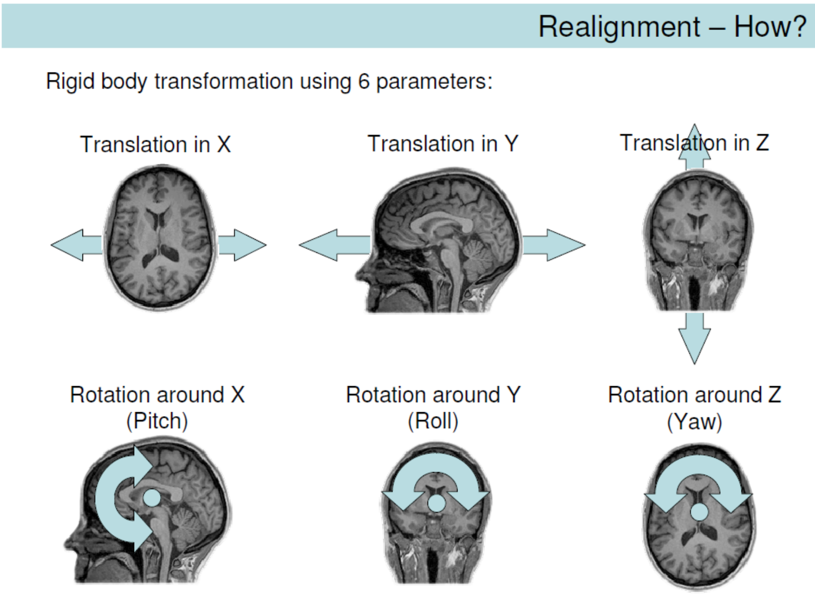
Slice Timing correction - SPM12's SliceTiming

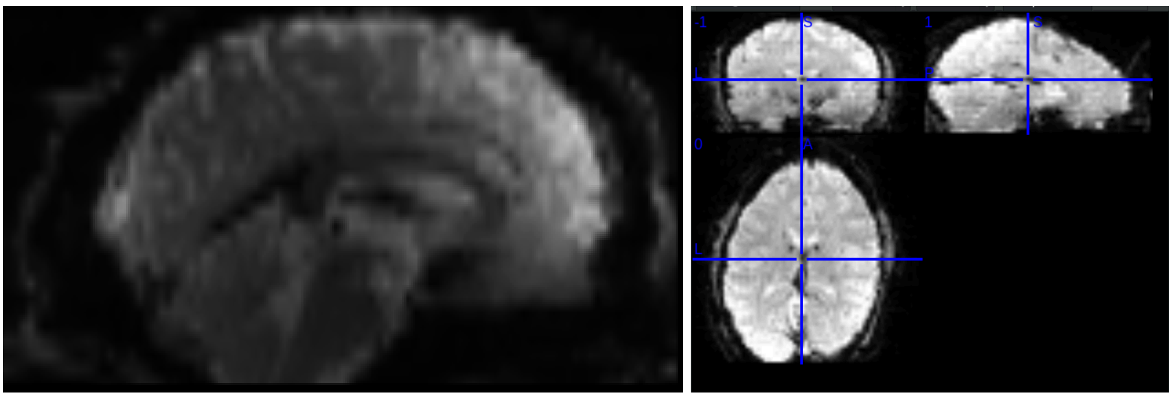
Slice Timing Correction is used to compensate for the time differences between the slice acquisitions by temporally interpolating the slices so that the resulting volume is close to equivalent to acquiring the whole brain image at a single time point.

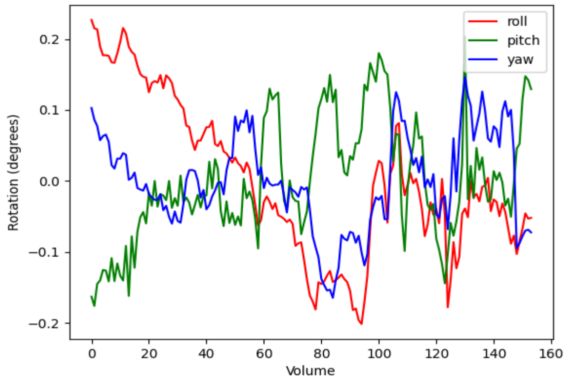
Reference: https://www.frontiersin.org/articles/10.3389/fnins.2019.00821/full

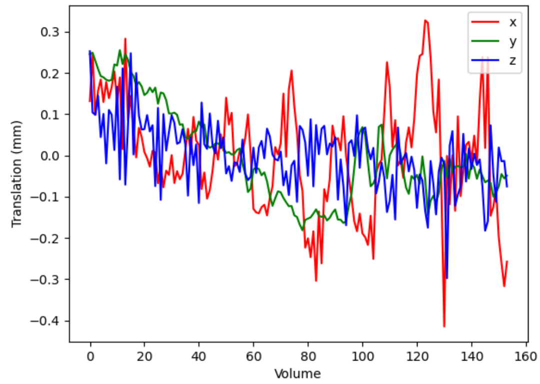
Motion Correction/Realignment - Friston24 Motion Correction

- Motion correction, also known as Realignment, is used to correct for head movement during the acquisition of functional data. Head movement can be characterized by six parameters: Three translation parameters which code movement in the directions of the three-dimensional axes, movement along the X, Y, or Z axes; and three rotation parameters which code rotation about those axes, rotation centered on each of the X, Y, and Z axes).
- Realignment usually uses an affine rigid body transformation to manipulate the data in those six parameters. That is, each image can be moved but not distorted to best align with all the other images. Below you see a plot of a “good” subject where the movement is minimal.
- The 6 parameters are further used to calculate the derivatives based on least squares which can be regressed to clean motion associated noise in the fMRI data.
- **Reference:** https://pubmed.ncbi.nlm.nih.gov/8699946/





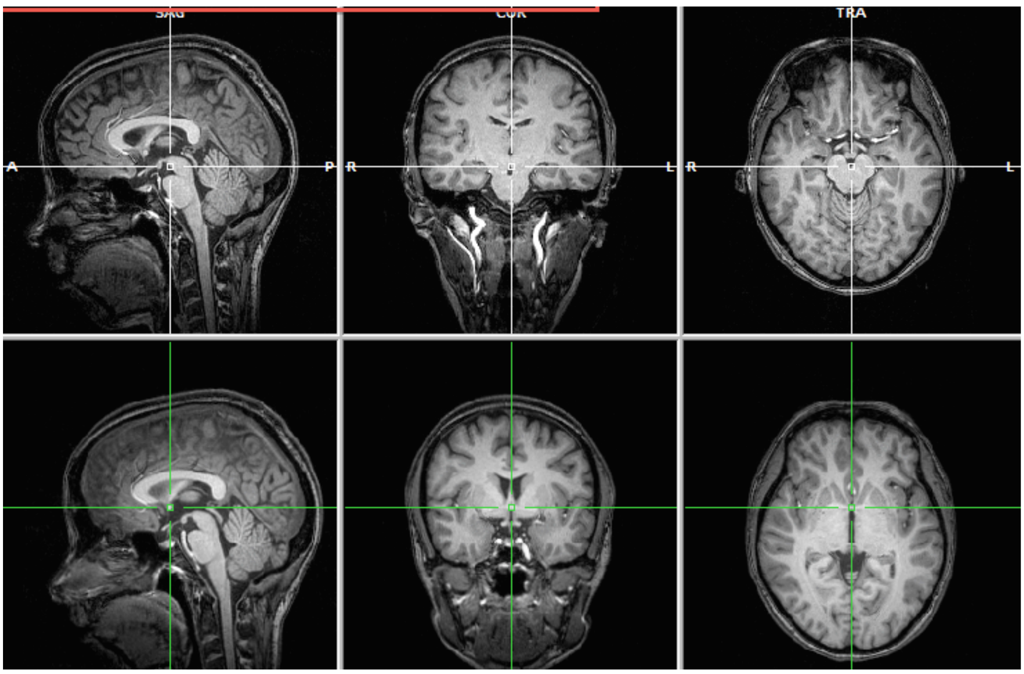




Automatic AC-PC Origin Correction

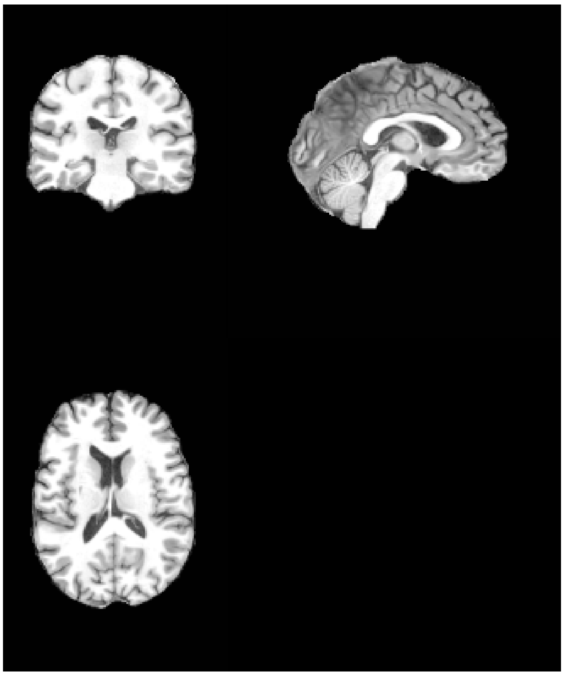
The sMRI and fMRI might have different origins in the 3D space which can lead to incorrect registration of the slices in the image. To avoid this, we perform automatic ACPC origin correction using SPM12 coregister estimate which estimates the origin to be set in the given MRI by comparing it with a manually ACPC origin corrected template.

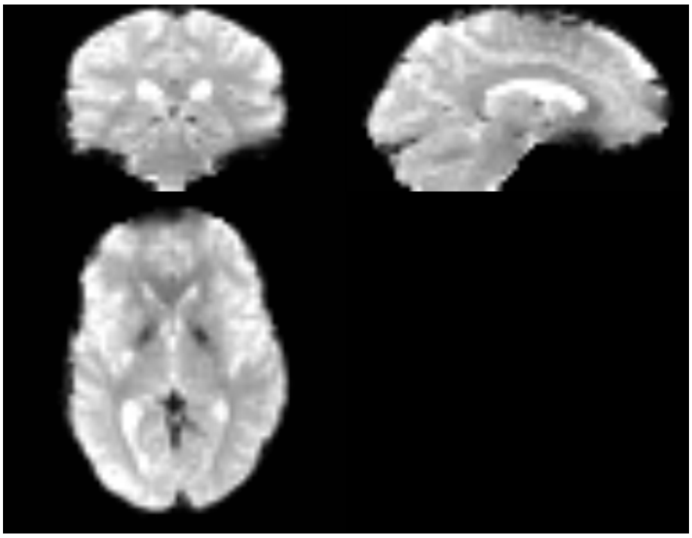
Reference:

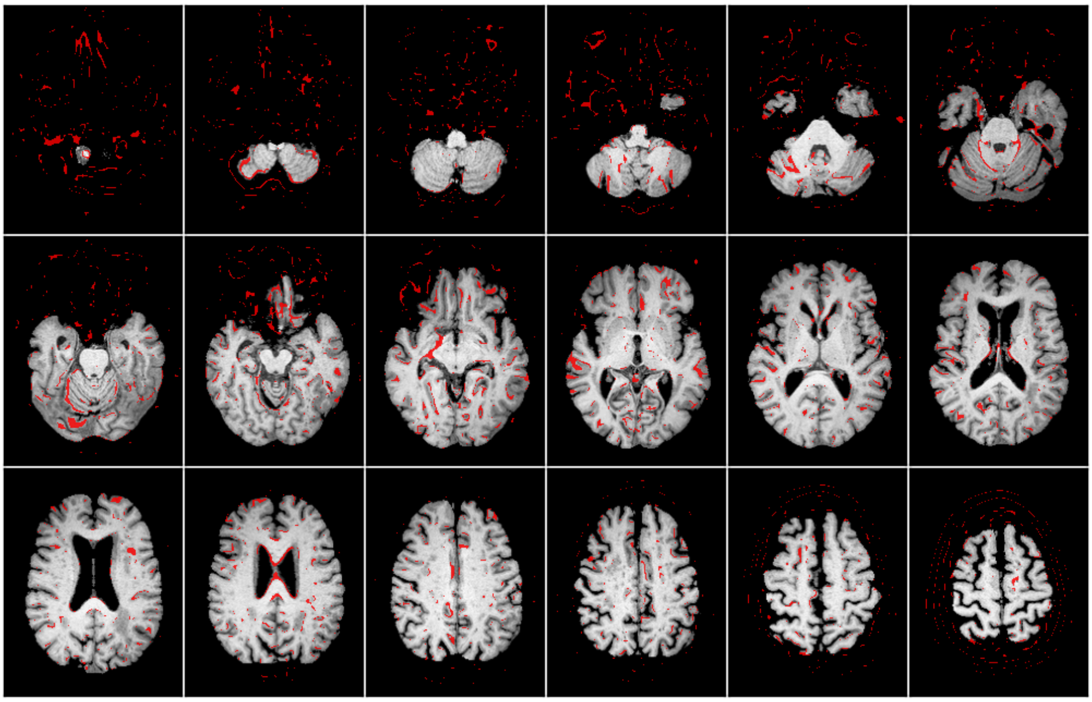


Skull stripping - UNET3D SkullStrip

Skull stripping improves the robustness of the registration to rs-fMRI and MNI normalization.



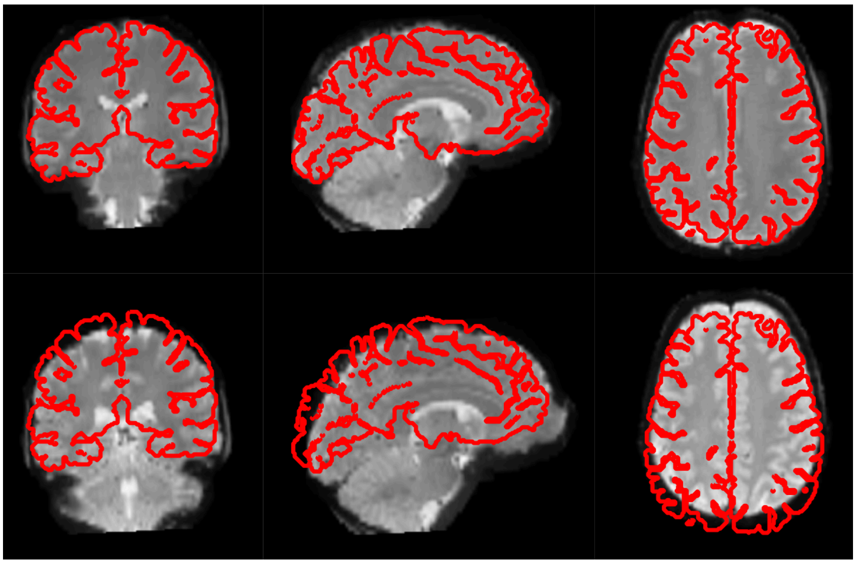




Reference: https://www.nature.com/articles/s41598-021-87564-6

Registration to MRI and Coregistration - ANTs Coregistration

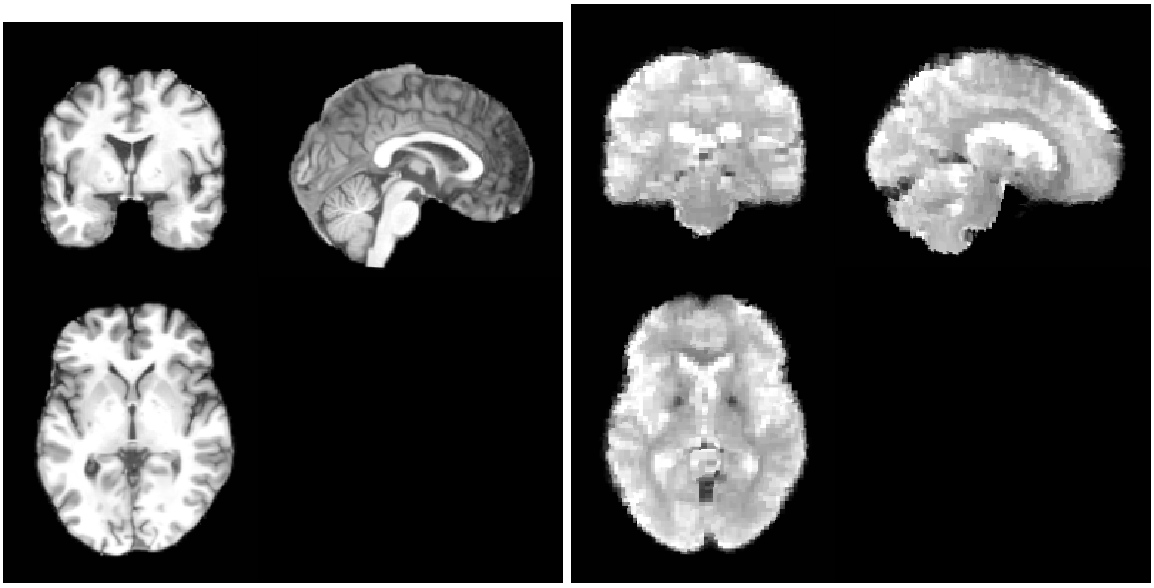
- Motion correction aligns all the images within a volume so they are 'aligned'. Coregistration aligns the functional image with the reference structural image. If you think of the functional image as having been printed on tracing paper, coregistration moves that image around on the reference image until the alignment is at its best. In other words, coregistration tries to superimpose the functional image perfectly on the anatomical image. This allows further transformations of the anatomical image, such as normalization, to be directly applied to the functional image.

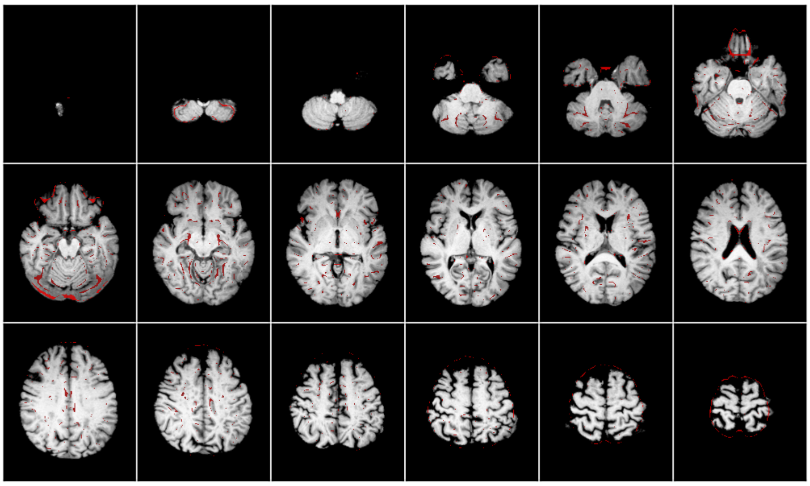


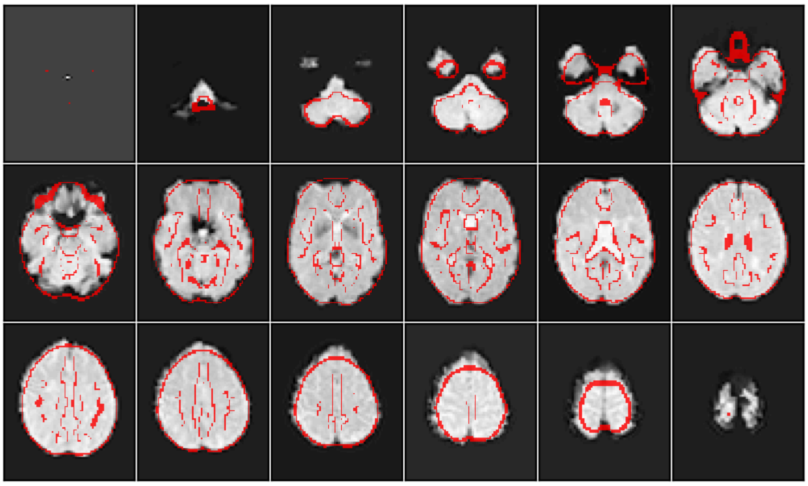
Reference: https://www.nature.com/articles/s41598-021-87564-6

MNI Normalization - ANTs Normalization

- Every person's brain is slightly different from every other's. Brains differ in size and shape. To compare the images of one person's brain to another's, the images must first be translated onto a common shape and size, which is called normalization. Normalization maps data from the individual subject-space it was measured in onto a reference-space.



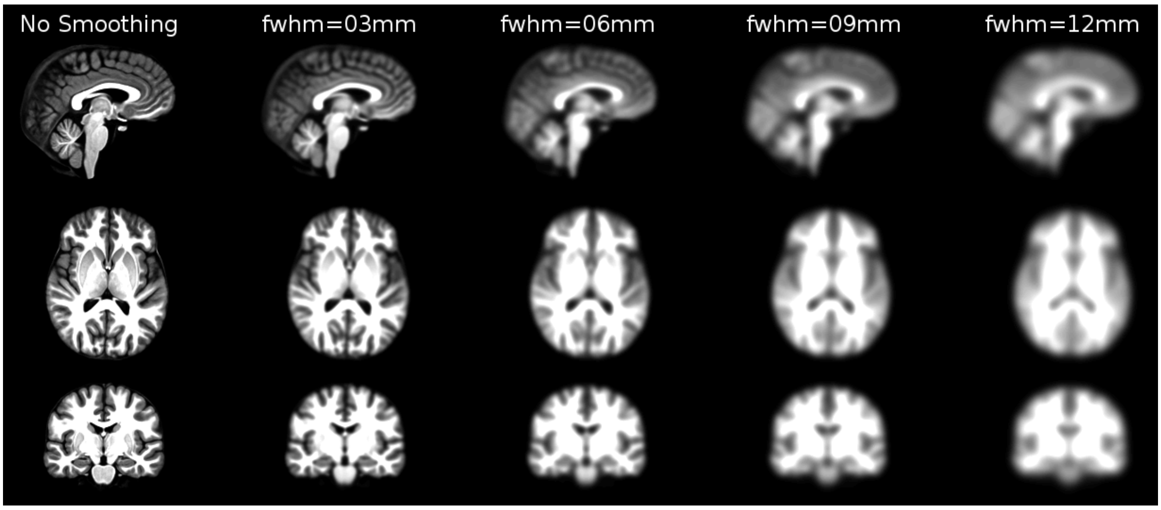


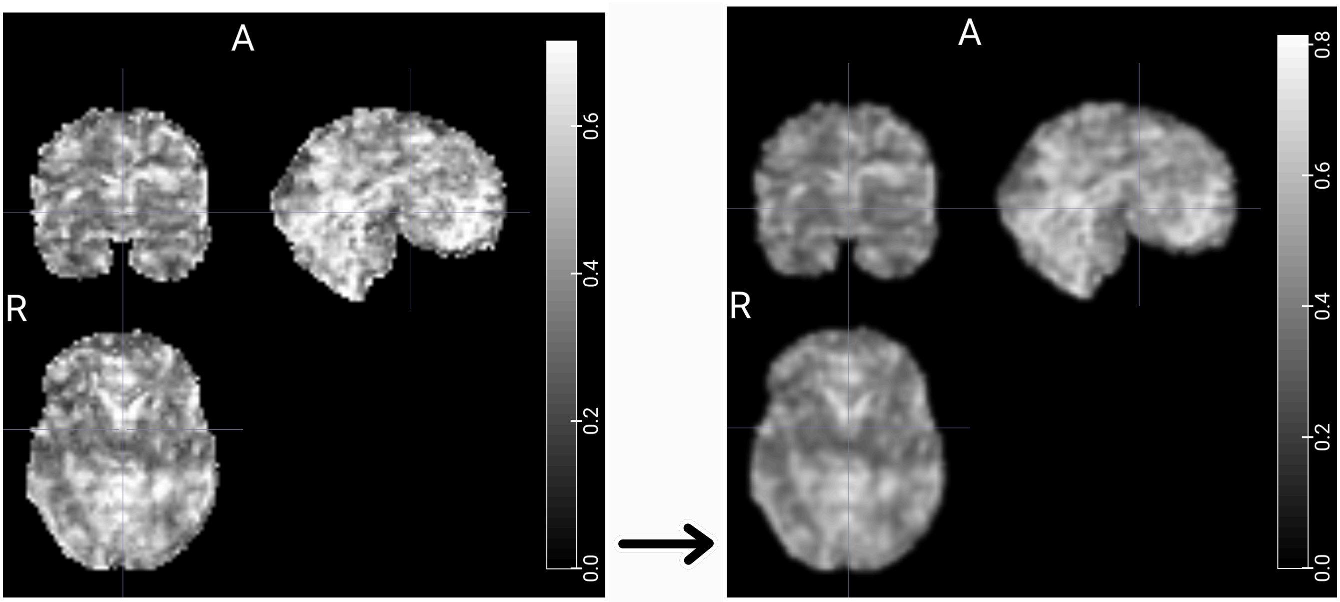


Reference: https://www.nature.com/articles/s41598-021-87564-6

Temporal Filtering and Spatial Smoothing - For ALFF, fALFF, and ReHo maps (0.01-0.1 Hz) and SPM's Smooth using FWHM of 4mm isotropy

- Low-frequency drifts are often thought to be caused by physiological noise as well as physical (scanner-related) noise. If not taken into account, these signal drifts substantially reduce the power of statistical data analysis. On the other hand, since neighbouring voxels can exhibit very different drifts, an additional high-pass filter is recommended.
- Smoothing increases the signal to noise ratio of your data by filtering the highest frequencies from the frequency domain; that is, removing the smallest scale changes among voxels. That helps to make the larger scale changes more apparent. There is some inherent variability in functional location among individuals, and smoothing helps to reduce spatial differences between subjects and therefore aids comparing multiple subjects. The trade-off, of course, is that you lose resolution by smoothing.

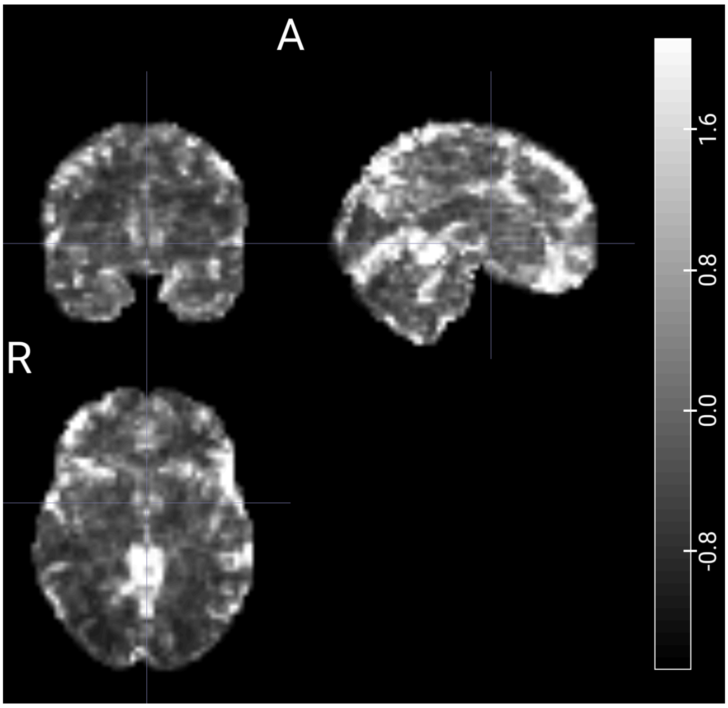




3) Final rs-fMRI preprocessing outputs and Quality assurance steps:

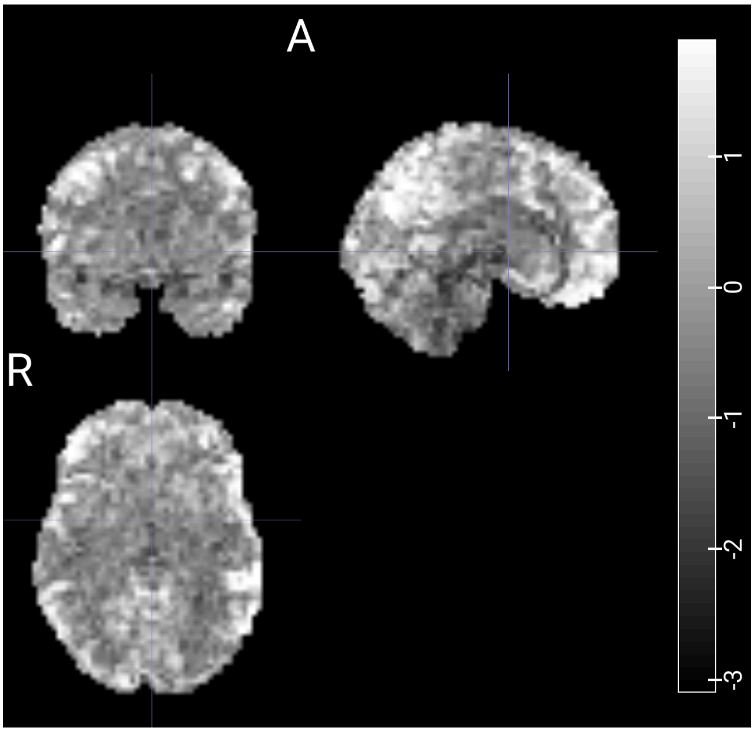
Spontaneous fluctuations in BOLD-fMRI signal intensity (from 0.01-0.1 Hz) of a resting brain, z-scored, and weighted across different metrics.

a) **Z-scored Amplitude of low-frequency fluctuations (ALFF) - smoothing, filtering, and runZScoring**



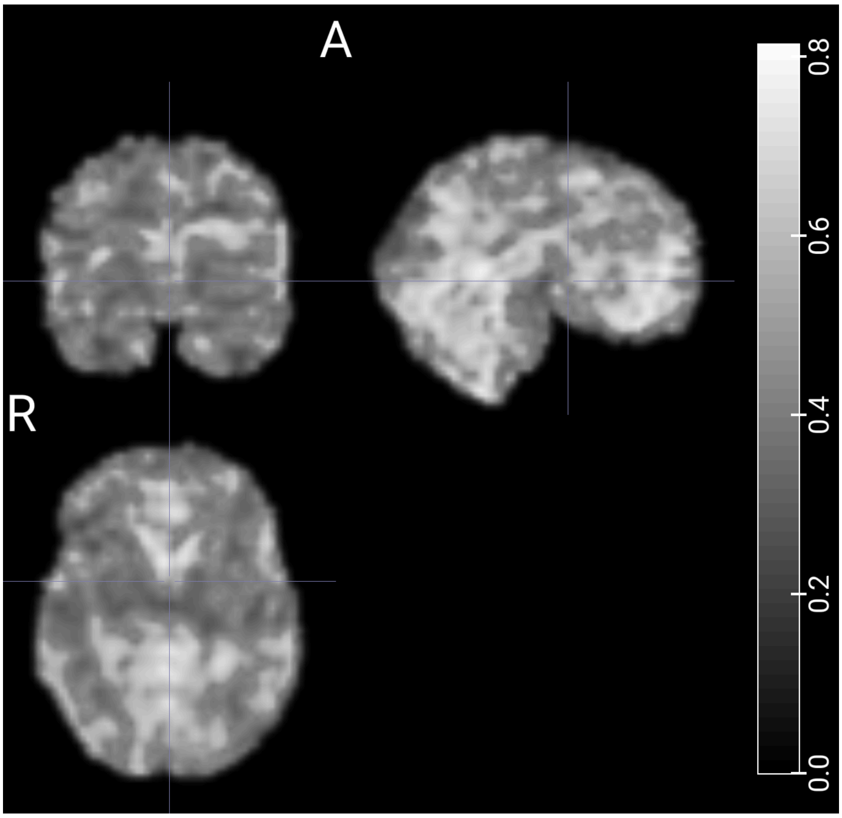
Reference: https://www.brainanddevelopment.com/article/S0387-7604(06)00154-9/fulltext

b) **Z-scored Fractional Amplitude of low-frequency fluctuations (fALFF) - smoothing, filtering, and runZScoring**



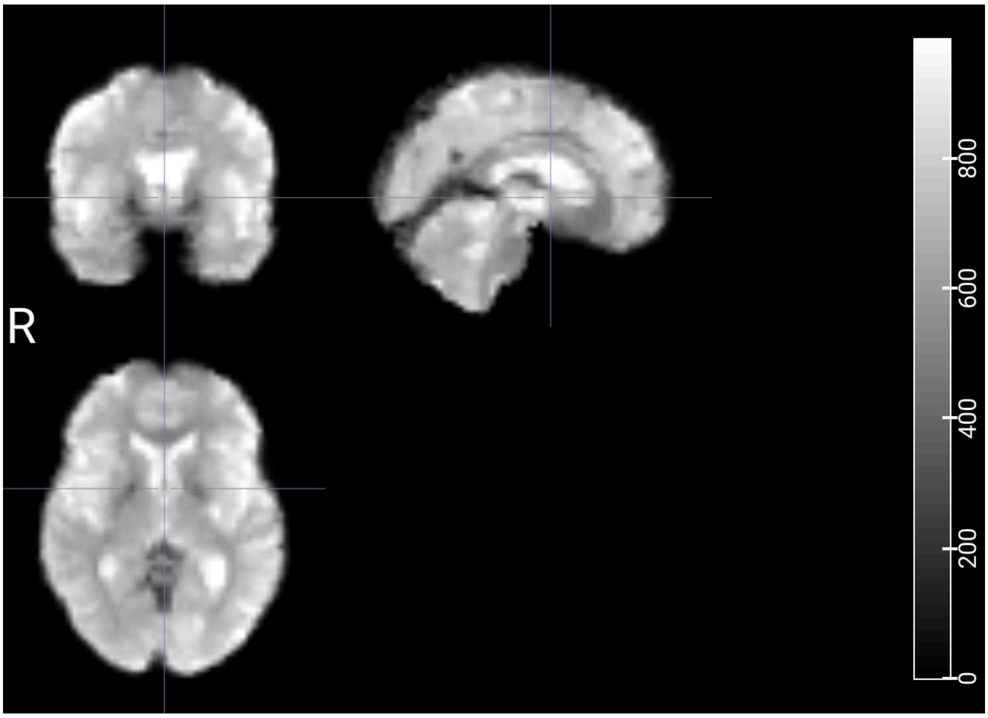
Reference: https://www.sciencedirect.com/science/article/abs/pii/S0165027008002458?via%3Dihub

c) **Z-scored Regional Homogeneity (ReHo) - clusterSize:27; filtering, smoothing, and runZScoring**



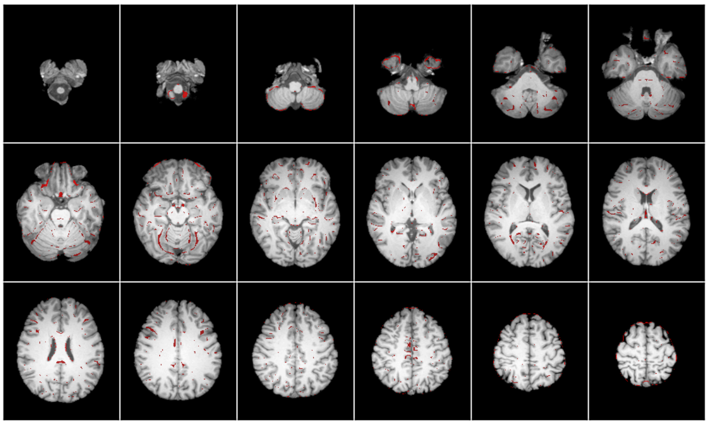
Reference: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5021216/

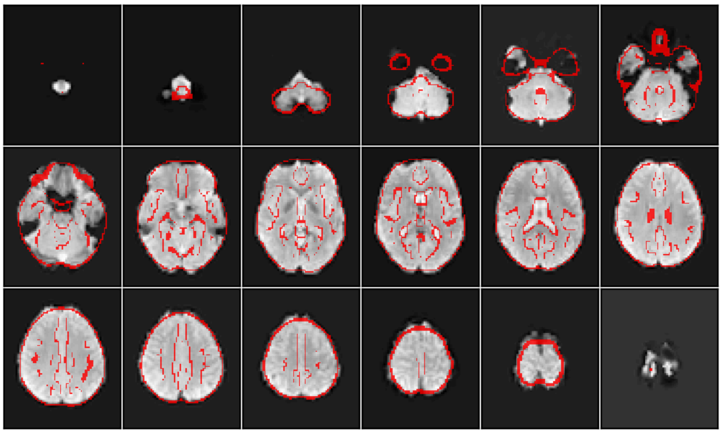
d) **4D Functional Connectivity file - multiple Timepoints**

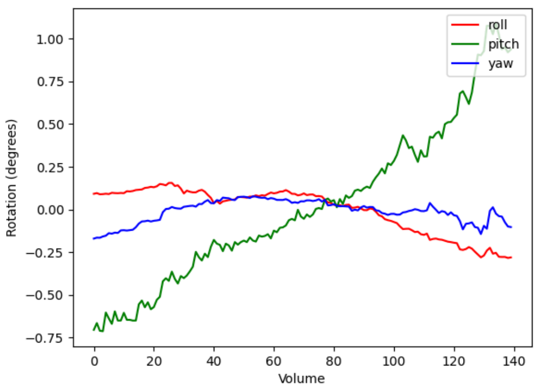


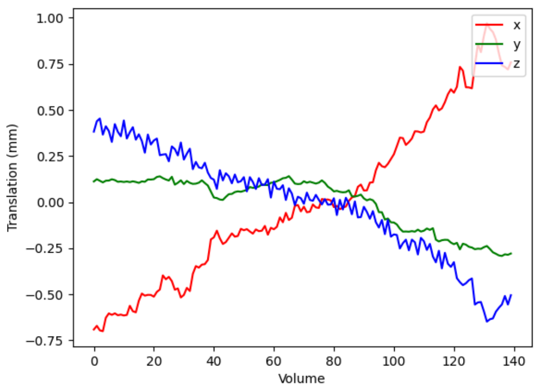
Reference: https://pubmed.ncbi.nlm.nih.gov/8524021/ | https://researchwith.njit.edu/en/publications/resting-state-functional-connectivity

e) **Quality Assurance/ Quality Control Images: Two normalization and two head-motion assessment images.**









4) Functional MRI Processing in Detail

VoxelBox has workflows for rs-fMRI and structural MRI processing.

It consists of three major series of preprocessing steps:

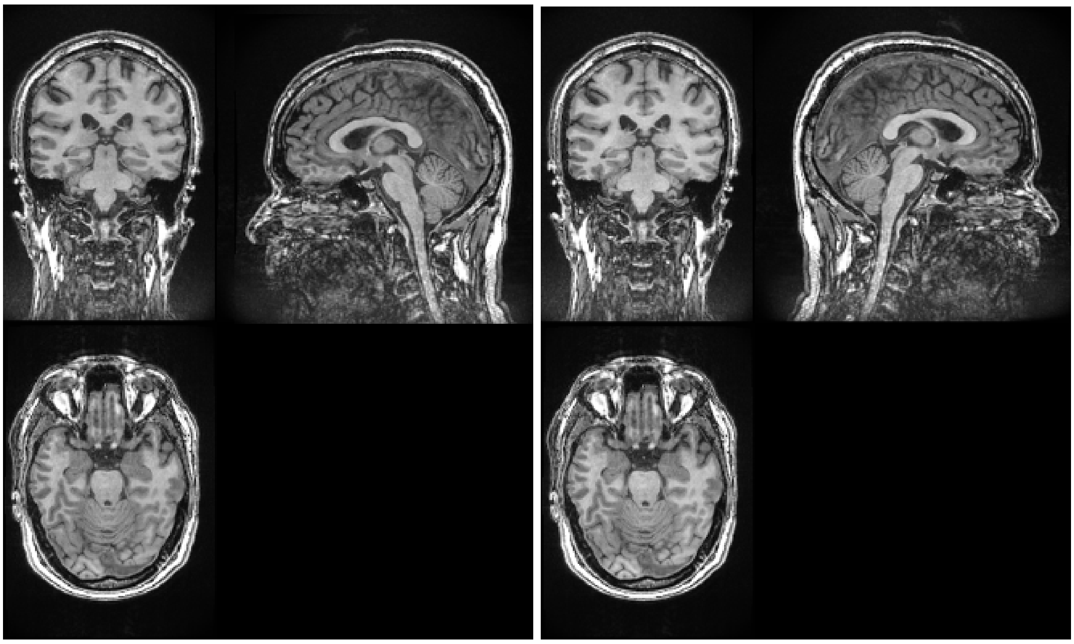
1. Structural MRI Processing - Minimal sMRI Workflow
2. Functional MRI Processing Part 1 - Pre sMRI Workflow for rs-fMRI
3. Functional MRI Processing Part 2 - Post sMRI Workflow for rs-fMRI

Structural MRI Processing - Minimal sMRI Workflow:

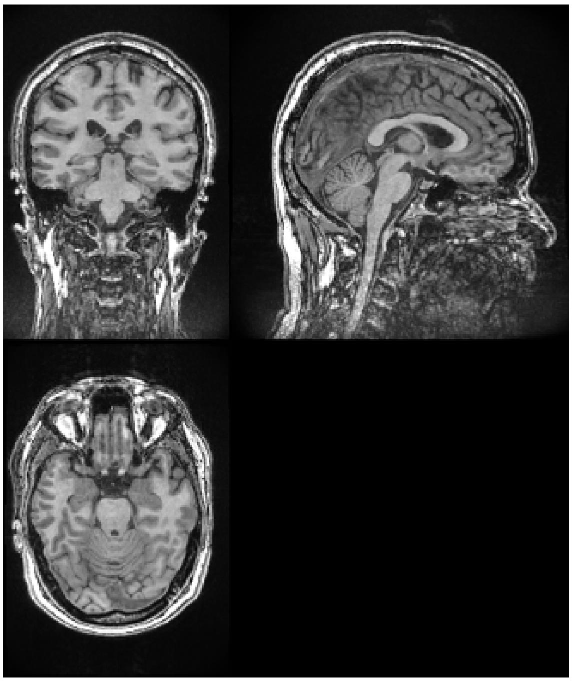
A minimal structural MRI preprocessing is done on the anatomical image prior to functional MRI preprocessing in order to ensure quality preprocessing of the functional MRI as the anatomical image is used in various steps of the fMRI preprocessing.

The following are the functions employed for the structural MRI processing:

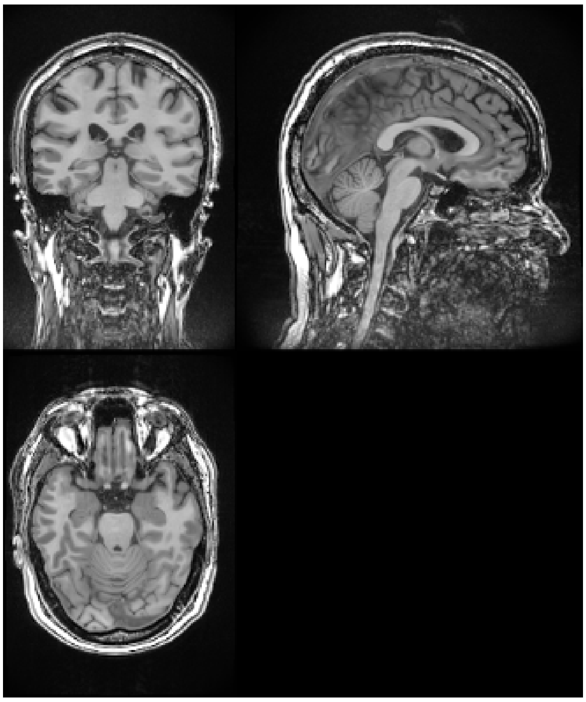
1. **Reorientation -** Reorientation changes the orientation or view of the MRI to bring all the MRI scans to a unified orientation. This step converts the input structural MRI image to the RAS (Right, Anterior, Superior) view/orientation, which is the standard orientation followed in medical image processing.



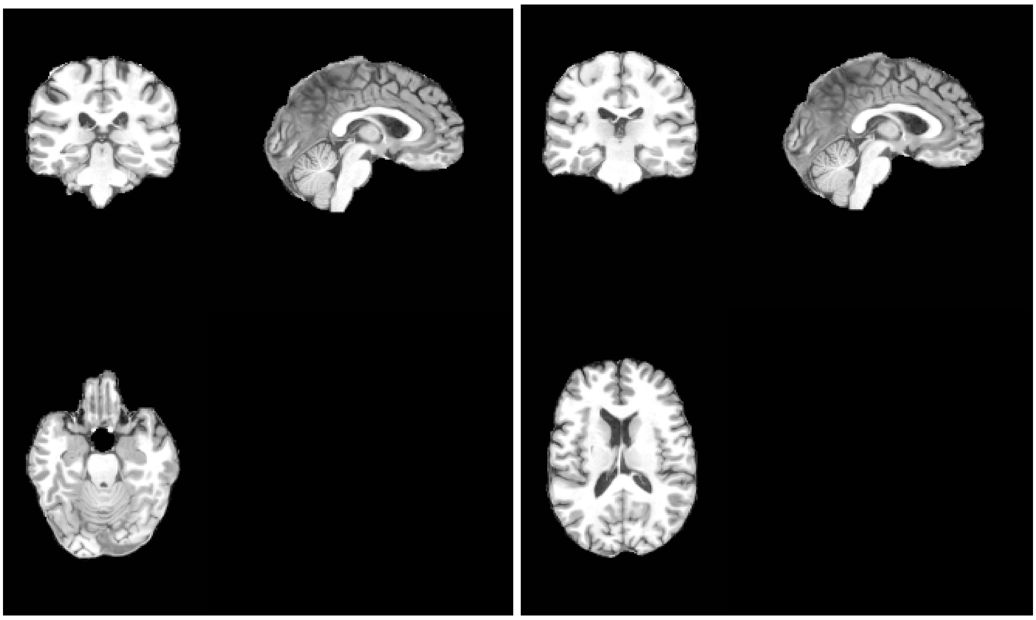
2. **Bias Field Correction -** Bias field signal is a low-frequency and very smooth signal that corrupts MRI images. It can be observed as a dark blurry noise that shadows parts of the MRI. ANTs N4 Bias Field Correction algorithm is applied to remove the bias field from a given structural MRI.



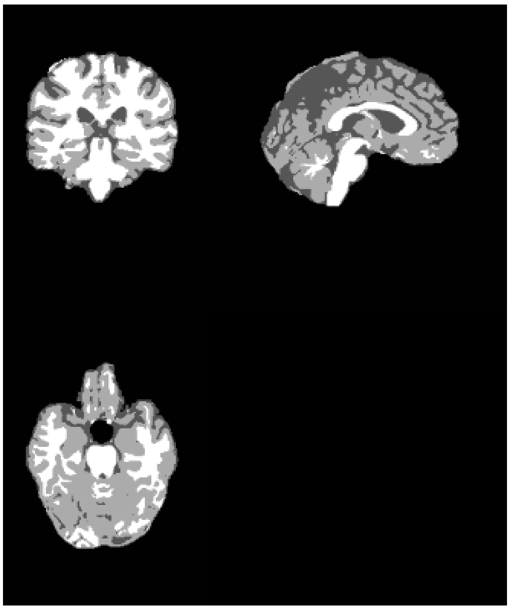
3. **Denoising -** MRIs usually contain noise that can be associated with the scanner which can be non-linear or gaussian. ANTs Denoising is applied to the image which removes the gaussian noise from a given image using Spatial Adaptive Filtering.



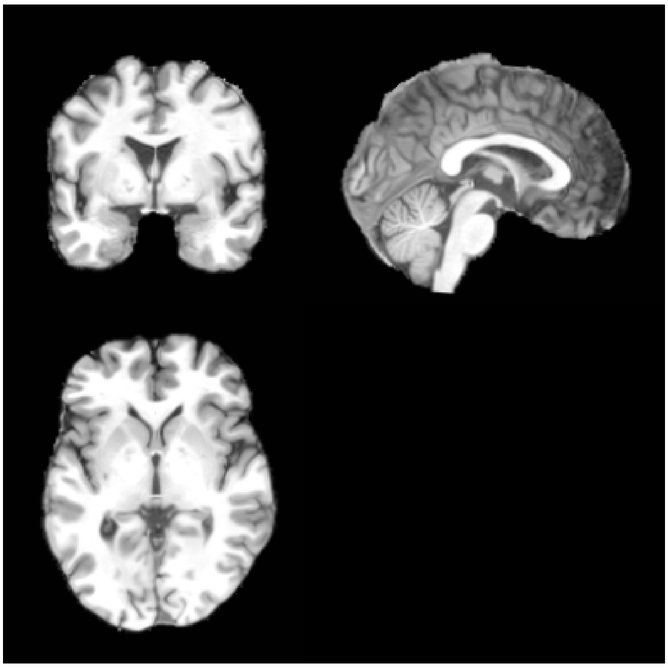
4. **Skull Stripping -** Skull stripping of T1w MRI improves the robustness of the registration to rs-fMRI and MNI normalization. VoxelBox uses a deep learning based approach for skull-stripping using UNET3D architecture, using pre-trained weights that was trained and evaluated over 14000 images by ANTsPyNet.



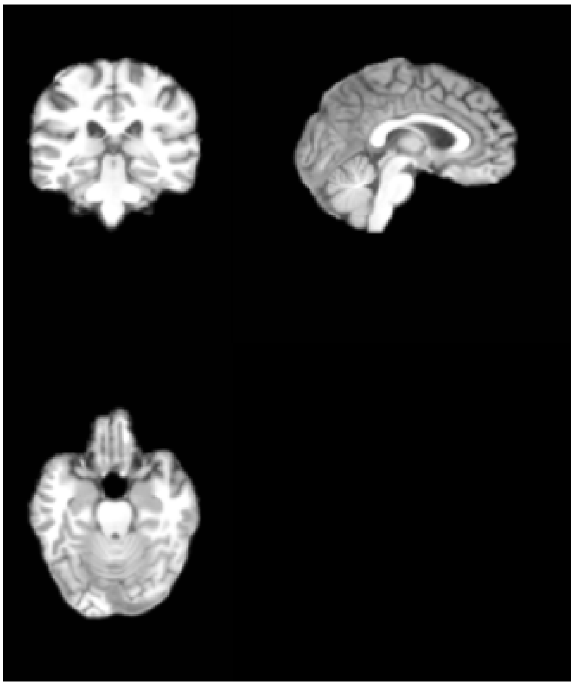
5. **Segmentation -** Segment the structural MRI into Gray matter, White matter, and Cerebrospinal fluid. ANTS Atropos is used for Segmentation.



6. **Normalization -** As every person's brain is slightly different from every other's and brains differ in size and shape, to compare the images of one person's brain to another's, we translate the MRI scans onto a common shape and size (MNI template).



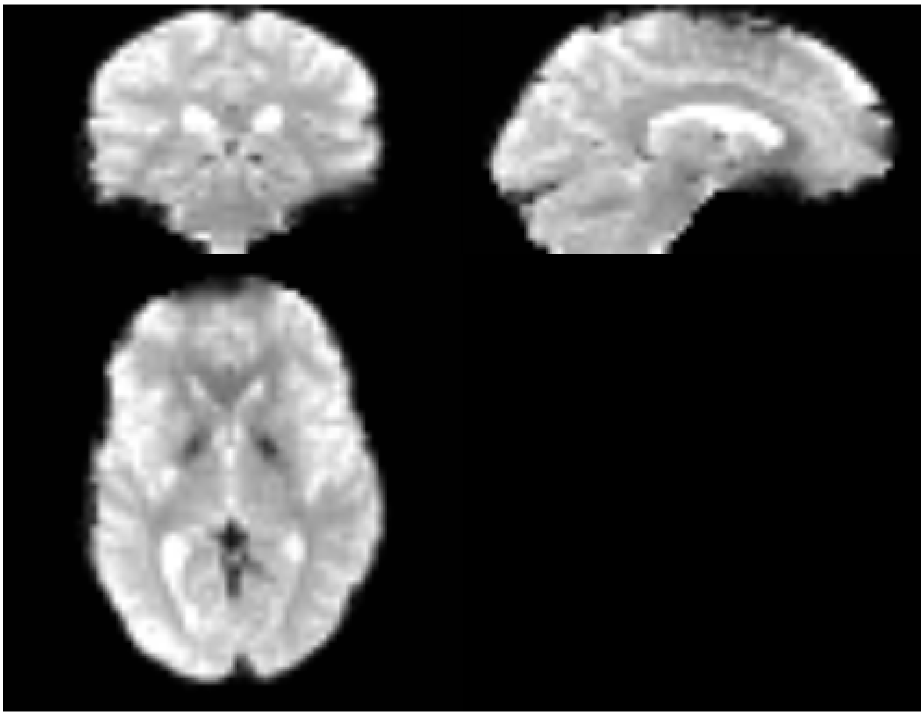
7. **Resampling -** Resampling is done to convert the MRI to a comparatively lower space or at 1mm isotropy which is the standard isotropy followed for T1 MRI scans.



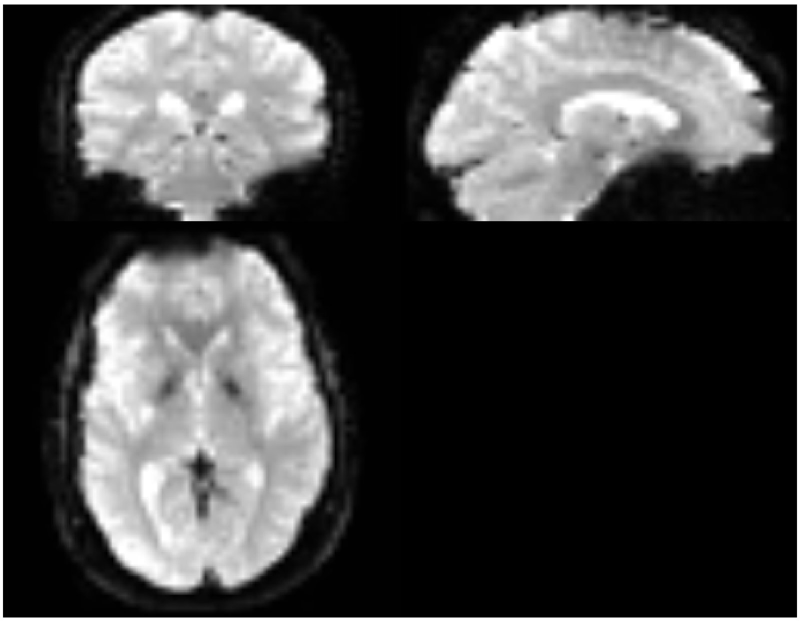
Functional MRI Processing Part 1 - Pre-sMRI Workflow:

A robust preprocessing pipeline is followed for the resting state functional MRI. The following are the functions employed for the functional MRI processing:

1. **Volume removal -** As it takes some time for the scanner field to reach steady magnetization, and for the participants to adapt to scanning noise, the first 10 functional time-series volumes are discarded.
2. **Skull Stripping -** Skull stripping of rs-fMRI improves the robustness of the anatomical coregistration and MNI normalization. VoxelBox uses a deep learning based approach for skull-stripping using UNET3D architecture, using pre-trained weights that was trained and evaluated on a private dataset by ANTsPyNet There are two pre-trained weights “BOLD” and “RobustBOLD”, with RobustBOLD having slightly better segmentation.



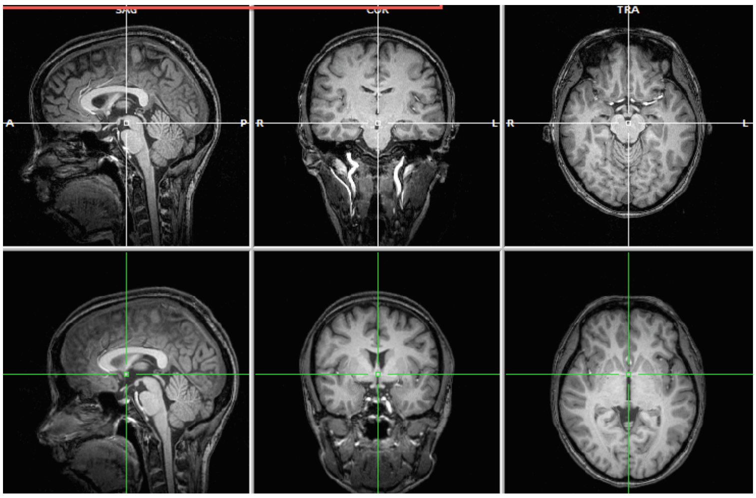
3. **Automated Slice Timing Correction -** To compensate for the time differences between the slice acquisitions, VoxelBox performs automated steps that temporally interpolate the slices so that the resulting volume is close to equivalent to acquiring the whole brain image at a single time point.This process is done using SPM12 and Matlab Runtime Compiler.



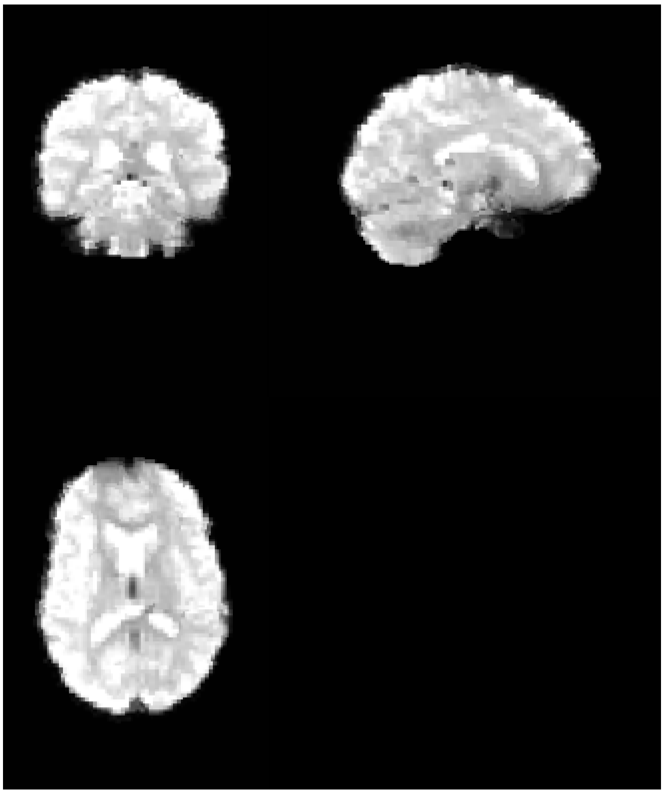
4. **Motion Correction -** Correct for head movement that usually occurs during the acquisition of functional data along the X, Y, or Z movement axes and X, Y, and Z rotation axes. This is done by default using the deep learning based motion correction framework, however, the pipeline also has capabilities to perform this using traditional approaches like Rigid Registration. Calculation of derivatives based on Friston24 head motion regression model to regress out motion related noise in the fMRI data.

Functional MRI Processing Part 1 - Post-sMRI Workflow:

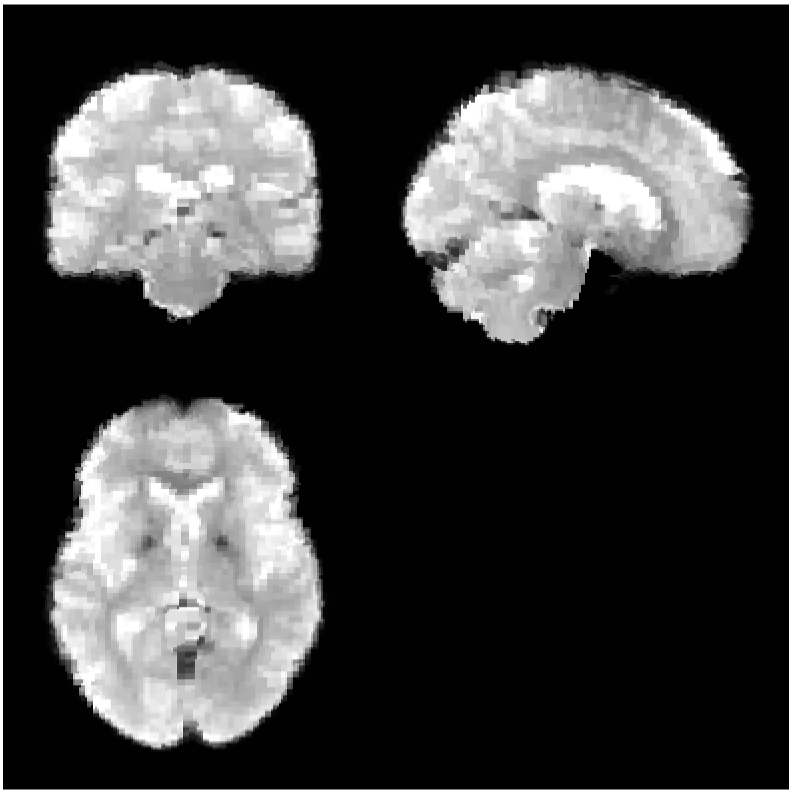
5. **Automatic ACPC Origin Correction -** Corrects the processed sMRI from Minimal sMRI processing workflow to set the AC PC Origin which would be used for coregistration.



6. **Resampling ACPC Corrected sMRI to fMRI Space -** For faster and efficient coregistration of fMRI with the sMRI, the sMRI is resampled to the sMRI space. The sMRI is resampled to the fMRI's voxel spacing which would be used for coregistration. x
7. **Coregistration with T1w Image -** Coregistration aligns the functional image with the reference structural image.

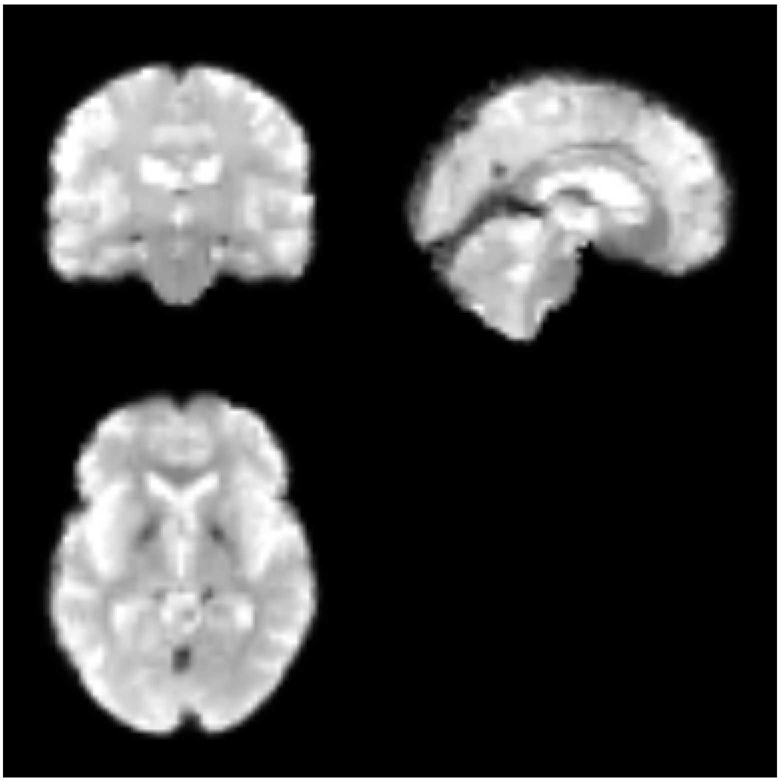


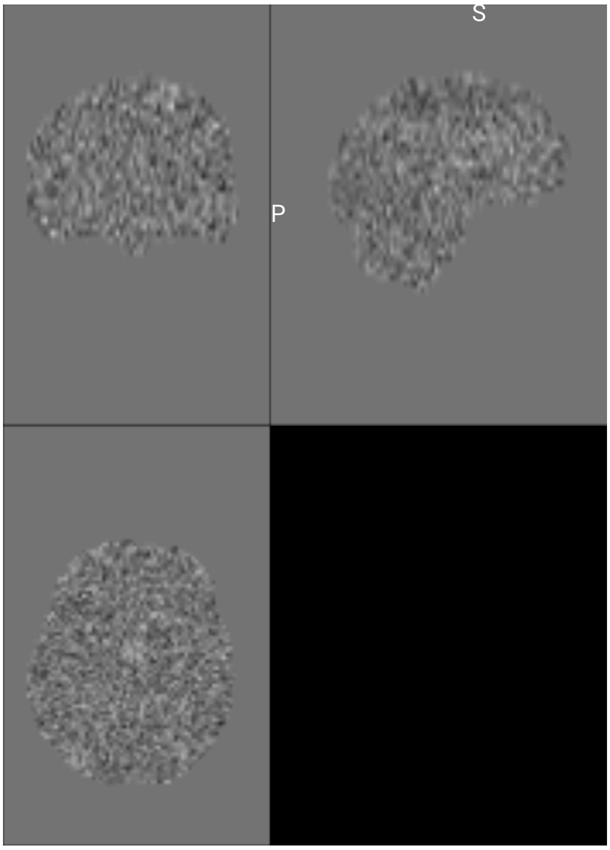
8. **Normalization -** As every person's brain is slightly different from every other's and brains differ in size and shape, to compare the images of one person's brain to another's, we translate the MRI scans onto a common shape and size (MNI template).



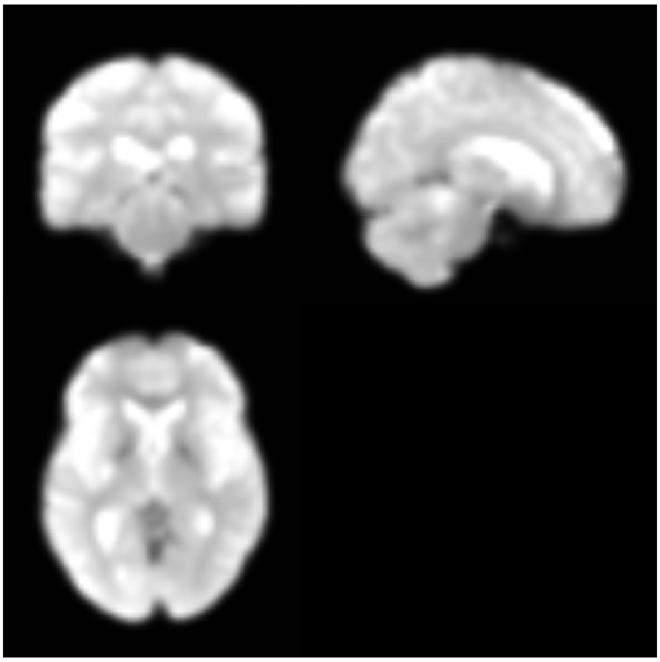
9. **Denoising:**
    a. The 24 motion parameters (Frisotn24 et al.) is regressed out of all the dynamic scans in the processed fMRI using a GLM (General Linear Model) based regressor.
    b. aCompCor regresses the top few principal components (PCs) (6 PCs in our case) within WM and CSF from the grey matter, thereby removing shared variation thought to represent noise using GLM. aCompCor is good at attenuating trends and sudden shifts in the data.

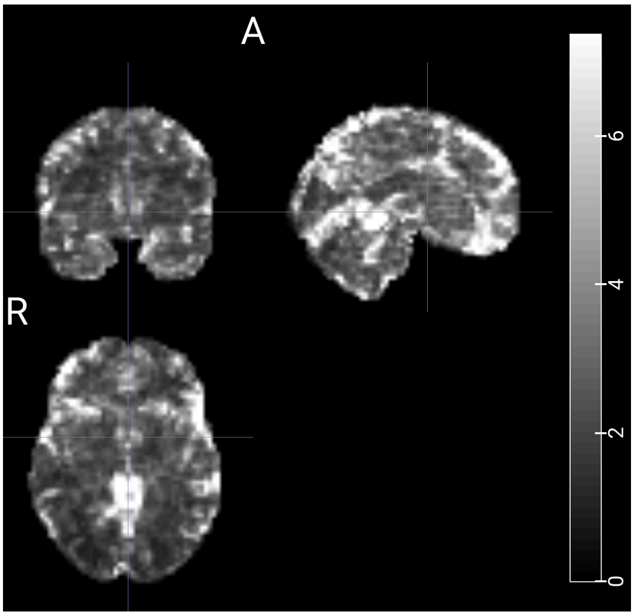
c. aCompCor is also used for estimating noise components based on availability of the tumor/lesion masks to denoise in tumor/lesion related areas in the image so as to reduce false positives. The pipeline also has “disconnection” capability (disabled by default) which removes all the signals from the tumor/lesion areas based on provided masks; the tumor/lesion area will be zero’d and will be treated as missing functional connectivities.
d. Furthermore, the fMRI is scrubbed for motion > 1.0 mm Framewise Displacement (FD) so as to remove volumes that have FD > 1 mm and only include volumes with less motion.
e. This would result in a denoised image free from motion distorted voxels, motion distorted volumes, anatomical noise, inducing voxels.

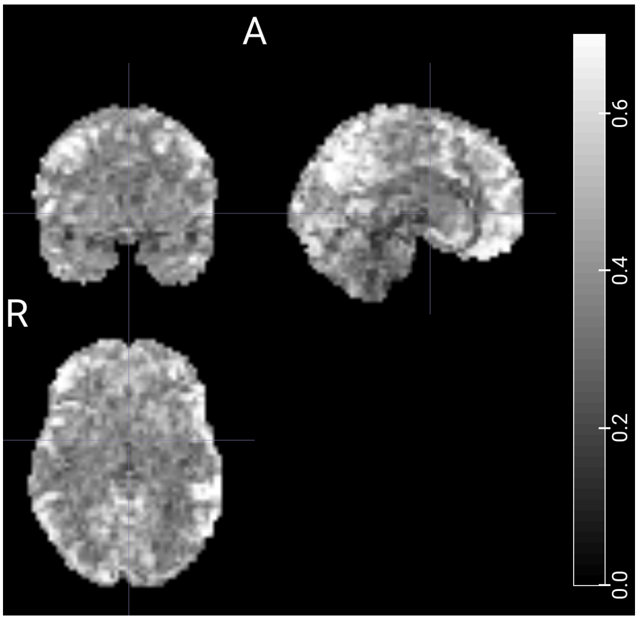




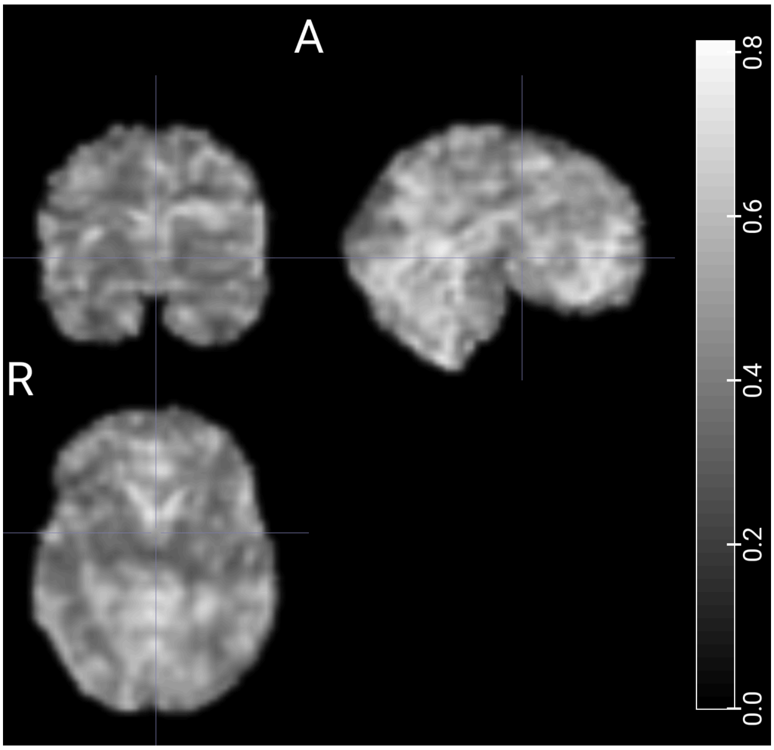
Smoothing & Band Pass Filtering:

1. **Spatial Smoothing & BPF -** Smoothing increases the signal to noise ratio of the data by filtering the highest frequencies from the frequency domain; that is, removing the smallest scale changes among voxels.

2. **ALFF & fALFF Maps -** Spontaneous fluctuations in BOLD-fMRI signal intensity (from 0.01-0.08 Hz) of a resting brain, z-scored, and weighted across different metrics.

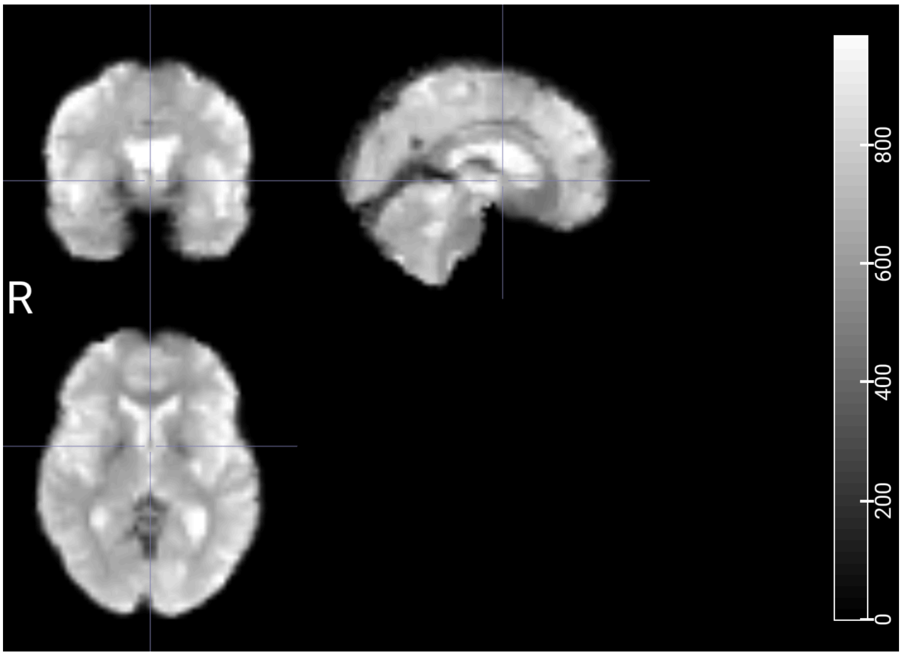




3. **ReHO Map -** Spontaneous fluctuations in BOLD-fMRI signal intensity (from 0.01-0.08 Hz) of a resting brain, z-scored, and weighted using a ReHo 27mm cluster Kernel.



4. **4D Functional Connectivity Map -** 4D Functional Connectivity file for extracting Functional Connectivity features. The file is band passed on 0.01-0.1 Hz.



Repo:
https://dev.azure.com/BrainSightAI/_git/voxelbox-docker?path=%2F&version=GBdev-package-v5.0.3&_a=contents

References:

Lenient and Stringent Motion Correction: https://pubmed.ncbi.nlm.nih.gov/23994314/
Slice Time Correction: https://www.frontiersin.org/articles/10.3389/fnins.2019.00821/full
UNET Model: https://arxiv.org/pdf/1505.04597
UNET for Skull-Stripping: https://www.mdpi.com/2076-3417/9/3/569
ANTsPyNet weights - Skull stripping - UNET3D SkullStrip: https://www.nature.com/articles/s41598-021-87564-6
Registration: https://www.nature.com/articles/s41598-021-87564-6
MNI Normalisation: https://www.nature.com/articles/s41598-021-87564-6
ALFF: https://pubmed.ncbi.nlm.nih.gov/19782143/
fALFF: https://www.sciencedirect.com/science/article/abs/pii/S0165027008002458?via%3Dihub
ReHo: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5021216/
4D Functional Connectivity: https://pubmed.ncbi.nlm.nih.gov/8524021/
https://researchwith.njit.edu/en/publications/resting-state-functional-connectivity
Friston 24: https://pubmed.ncbi.nlm.nih.gov/8699946/
Estimation of components in ACompCor : https://pubmed.ncbi.nlm.nih.gov/21889994/
Bandpass filtering : https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3759585/
When to apply bandpass filtering (Before or after nuisance regression) : https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6865661/
Why we do not use Global Signal regression in our pipeline : https://pubmed.ncbi.nlm.nih.gov/18976716/
How to select optimum number of motion regression components and thresholding : https://pubmed.ncbi.nlm.nih.gov/23994314/
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